we look at how many actually presented with otorrhea and perforation at baseline, there were more patients in the PRSP group than in the overall group.

Next.

So next I'd like to move on to discuss the assessment and then look at the actual response results. There were four additional patients who were included in the FDA analysis as clinical failures, and these patients had been considered successes in the sponsor's analysis.

And the reason that they had been added into the FDA analysis as clinical failures was based on an assessment of the clinical presentation that was consistent with the protocol definition of acute otitis media either at the time that they presented, either at the on therapy visit or at the test of cure visit.

However, as I mentioned, they were considered successes in the sponsor's analysis based on the investigator assessment, and because the investigator felt that they were clinical successes, they were not administered any additional anti-infective agents.

So I'd like to present the overall clinical responses for the PRSP population at the test

of cure visit in the FDA population.

In the protocol group, we see that 14 of 34 had a favorable response with a percent of 41.2, and the 95 percent confidence interval around this point estimate falls between approximately 25 and roughly 60 percent, and we see that in the ITT population the numbers not unexpectedly are lower than those in the protocol group.

Next. Oh, actually hold on one second.

So it could be argued, I guess, because of the addition of the four patients into the FDA analysis based on strict inclusion of these patients from the protocol was a little bit conservative, and so what I'd like to present in the next slide are just the results with the four patients considered as successes.

Next.

And this is essentially the results that, you know, you would see from the sponsor's analysis. In the protocol population, we see that rather than having -- you know, the four failures have been included here. So instead of this being 14, this is now 18, and the overall clinical response is approximately 53 percent, and the confidence interval around that point estimate ranges from about 35

percent to 70 percent.

And similarly, with the previous analysis the results that you see in the ITT population are a little bit lower.

Next.

In this slide what I'd like to just present is the results broken out, and this is FDA results broken out by penicillin MIC to give you a sense of how -- what the clinical responses were, and clearly we see that in patients with an MIC of four in either the per protocol or the ITT population, those clinical responses at test of cure were lower.

Next.

And to give, I guess, some more complete information because the indication being sought is not just for PRSP but for all acute otitis media pathogens, when we look at the clinical response in patients that are non-PRSP, we see that in the ITT population, the overall clinical response is -- sorry -- in the protocol population the overall clinical response is approximately 78 percent. For H. flu. about 68 percent of the patients had favorable response at test of cure in the protocol population, and for M. catarrhalis it's approximately 56 percent.

Next.

So based on the results that we've seen from the previous slide and just the overall results that we're seeing for the PRSP, it was of some interest to us to try to get some sense of, you know, we know there are risk factors that we've talked about here that are associated with both recurrence and both with PRSP. So we were interested in just looking at this information to try to see whether there was any type of relationship in terms of the non-PRSP versus those with PRSP and the overall clinical response when you control for these factors.

These are clearly not all of the risk factors that have been identified or that we've been discussing today, but the reason we chose, one, the ITT population and also these particular two risk factors is that these are the ones that gave us the most information that included the most patients in terms of trying to do this analysis and get some feel for what was actually going on.

And before going on, I'd like to just note that, you know, several of these cells here do have small numbers. So I guess we have to take that into consideration as we look at these results.

But to just try to walk you through, in terms of the clinical response for non-PRSP isolates

versus those that had PRSP, when you control for either prior antibiotics -- sorry -- prior acute otitis or patients of young age, we see that, you know, in this first risk subgroup there's too much of a difference in terms of what you're seeing in the clinical response between those who are in the non-susceptible population, nonresistant population versus those in the resistant group.

And as we march through the other subgroups, there seems to be a difference here in this particular subgroup in terms of what you're seeing in the PSSP group versus the PRSP group.

And then in the highest risk subgroup, we see that there is the greatest difference. This is the biggest difference that you're seeing between the clinical response when you control for these subgroups versus in those with susceptible organisms versus those with PRSP.

So I wanted to just, I guess -- we've discussed some of the information about some of the failures in terms of some of the slides I've presented earlier, but I wanted to try to address the issue of time to failure, and these results are based on the 20 failures that were assessed in the FDA population, but I've also just induced some information about time to

failure in patients if you excluded the four failures in the FDA analysis.

So in looking at these results, this information and trying to get some feel for at what point int he study where patients assess as clinical failures by the investigator, we see that of the 20 patients that were considered clinical failures, 11 of them were assessed either at day 17 or before.

And what I'd like you to note is that this number, this lower than day 17, includes patients that could have been assessed as failures as early as at the on therapy visit.

There were nine out of the 20. The remaining 45 percent who were assessed as failures beyond the day 18 time of the study, and the numbers, if you exclude the four failures in the FDA analysis, are very similar based on the sponsor's numbers.

In terms of the age distribution of failures, I looked at this to try to get a feel for how many, what was the age of patients that actually failed in the study, and all the patients were under two years of age that failed. The youngest patient that failed was six months of age, and 12 out of 20 patients that failed in the FDA group were under 12 months of age, whereas ten out of 16 -- and, again,

these percentages are essentially the same -- were under 12 months of age.

Next.

So I'd like to move on now to discuss the bacteriologic response in the PRSP group. First off, looking at the results at the on therapy visit, and this slide summarizes the results for all patients who met a definition of having PRSP and also the subsets of patients who either had an MIC of two or those who had an MIC of four.

And as we look across, we see that in the protocol population, the overall bacteriologic response at the on therapy visit in patients with PRSP was approximately 94 percent. The range for both groups, subsets of patients who made up this group was from 85 with those in -- 86 percent with an MIC of four to 100 percent with an MIC of two.

And similarly, you know, very good results that you've seen here with the ITT population.

However, as I've mentioned several times, in the FDA analysis the bacteriologic response was assessed, presumed from the clinical response.

Next.

And we presumed the response from the clinical response because in most cases we didn't have

information unless we -- there was some information available, and this was the case that we did actually have information on taps that were done later on on two patients.

There were two patients who had both H. influenza and PRSP isolated at baseline, and in both patients, the MIC for the pen. resistant Strep. pneumo. was two.

These patients both got retapped at the time that they failed, and when they were retapped, there was no demonstration of PRSP in their repeat culture. However, the H. flu. persisted.

And in addition, in making an assessment or in looking at this bacteriologic response at the test of cure, the two patients that were assessed as clinical failures in the FDA analysis at the on therapy visit had negative taps at the on therapy visit.

So these two patients plus those others were included in considering the overall bacteriologic response at test of cure in the FDA population.

Next.

So these results summarize what that eradication or presumed for the most part for the majority of the patients, except those two that I've

mentioned, what that presumed eradication rate was at test of cure and, again, summarizing the results by overall PRSP group and also subsetted by the particular MIC of the patient population.

So in the per protocol population, at test of cure, these are presumed eradication rates. We see that overall it's approximately 53 percent of patients had a favorable response at the test of cure visit. Not unexpectedly, because the two patients that had follow-up taps had MICs of two, they fell into this group, and so these numbers have increased, but the overall in the patients with the MIC of four haven't really changed.

And similarly, the results in the ITT population are a little bit lower than what you see in the per protocol group.

Next.

So I wanted to just summarize a little bit about what we're seeing of the results in terms of clinical response as it relates to bacteriologic failures.

There were 34 patients who were in the clinical protocol group at test of cure. There were two bacteriologic failures from the on therapy visit. Of those two, one was assessed as a clinical success,

and the other one as a clinical failure at the time of test of cure.

The other 32 patients had no growth of their PRSP at the time that they were retapped at the on therapy visit, and of those, when they were followed through to the test of cure visit in terms of their clinical response, we see that 13 out of the 32 were actually assessed as clinical successes at that time.

Next.

So to summarize where we are in terms of the results as we've seen them, the clinical response in the pen. resistant Strep. pneumoniae group at the test of cure based on the FDA analysis overall was 41.2 percent. The 95 percent confidence interval around this point estimate ranges from 25 to 59 percent.

The bacteriologic response for the pen. resistent Strep. pneumoniae group at the on therapy visit was approximately 94 percent.

The presumed bacteriologic eradication rate at test of cure, and again, reiterate that it's presumed for almost all of the patients, was 53 percent.

Next.

And when we looked at the clinical response broken out by penicillin MIC, again, we see that overall the clinical responses in patients with an MIC of four are lower than those seen with an MIC of two.

So I'd like to move on now to just briefly discuss some of the safety information, and this is from the bacteriologic study.

There were no deaths in that study out of the 521 patients that qualified for this safety analysis. There were seven patients who had at least one serious adverse event, and of those seven, two had a report of diarrhea, and the other serious adverse events are listed here.

Next.

Of the 521, 24 were withdrawn because of an adverse event, and the main reason for withdrawal out of those 24 patients was diarrhea, followed by vomiting, and the other reasons for withdrawal of these patients as a result of an adverse event are listed here.

Next.

And we know that diarrhea is associated or -- sorry. The other way around -- amoxicillin and clavulanate have been associated with diarrhea. So

we're interested in looking at diarrhea in this population to just get a feel for whether the amount of diarrhea that we were seeing here was significant.

The definition of diarrhea as it was in the protocol was as follows: three or more watery stools in a day; two watery stools on two consecutive days; or any report of an adverse event of diarrhea.

So of the 521 patients that qualified for the safety group, 70 had reported an episode, fell into this category that met the definition for protocol defined diarrhea, and this was 13.4 percent of the patients.

Next.

So to give a summary of the safety information from the bac-T study, there were no deaths in the study. Few patients had serious adverse events. Diarrhea was the most common reason for withdrawal, and protocol defined area was seen in 13.4 percent of the patients.

Next.

So I had mentioned at the outset that there were some issues that we grappled with in terms of reviewing this application, and I wanted to just bring those out here, and some of these will come forth in the way of the questions, you know, as you go

into your discussion and in some way are replicated in some of the questions that you will be addressing.

First, we noticed that there was an inconsistency between the on therapy bacteriologic responses and the clinical outcomes that we're seeing at test of cure.

The next issue was that the clinical responses at the test of curve visit, we were having difficulty trying to interpret these results without any additional information either about the natural history of acute otitis when it's due to PRSP or any information in terms of any other agent and how that agent actually fared in treating patients with acute otitis due to PRSP.

Next.

So we went to the literature to try to, I guess, get a sense of what might be out there in terms of placebo controlled trials, and clearly, you know, there have been a couple that have been discussed, and Dr. Kaleida's paper has been discussed, and this was one that we dug up to basically try to get some information. Clearly, it's not the only one, and this paper was one by Halsted, et al., published in 1968 and titled "Otitis Media Clinical Observations Microbiology and the Evaluation of Therapy."

And the reason that, I guess, we felt this was of some interest was that it was a placebo controlled trial and did have some bac-T data.

There were 66 patients with a baseline pathogen, and of those 83 percent were under two years of age, which is similar to, you know, the patient population that we're kind of interested in here. Sixty-one percent had Strep. pneumoniae.

However, I would like to note that there was no susceptibility information provided at all in terms of any of these isolates. So there are no conclusions that we can draw about, you know, any of the responses that we see.

Study visits were done two to three days after study entry, and also patients were seen later on, 14 to 18 days after study entry.

Next.

So when we looked at specifically the results for the placebo group, there were 19 patients who had baseline pathogen that came back for follow-up visit. At the first visit two to three days out when they were assessed clinically, 13 of the 19 patients showed some clinical improvement, and there were four failures.

When the patients were followed out to day

14 and 18, either through days 14 through 18, one of the patients actually fell out because he had a pathogen which was not -- they were not including in terms of an isolate that they were considering in their studies. So there were 18 patients left over, and 14 of those were considered clinically well.

However, as I've mentioned, because we don't really have, you know, any information about susceptibilities. This is just one paper, has some placebo information in it, but doesn't really give us a very good feel in terms of the issues that we're grappling with here in terms of PRSP.

Next.

So this is a summary slide to basically reorient us to where we are in terms of what we know, the information that we have.

We know that this is what Augmentin ES has done, end of therapy results versus test of cure results. However, in terms of trying to, you know, make an assessment about these results, and as I said, this is the issue that we were grappling with just in terms of lack of information to try to make an assessment about the activity of Augmentin ES against PRSP. We don't really have any information about placebo.

Next.

The other issues that were raised by the review were the consideration of an empiric indication for acute otitis media when PRSP is suspected, and the seven to one formulation treats acute otitis media due to H. flu. and Moraxella catarrhalis.

And then the issue which has been raised already and will be part of your discussions is the selection of the timing of the assessment of both the bacteriologic and clinical outcomes.

Next.

So this basically would lead us to the questions which I'll review, and then we'll have a presentation to follow, and then these would be the questions that would take us into the discussion period after the next presentation.

Question one, to assess the clinical response in an acute otitis media trial targeting PRSP, what is the relevant test of cure? Is it the end of therapy, which is typically a few days after the last dose, or is it the later follow-up usually done one to three weeks after the patient takes the last does?

And would your answer be different in an acute otitis media trial of all comers, meaning that

it's not specifically enriched for PRSP?

And please explain just means please discuss.

Next.

Question two, to assess the microbiologic response in an acute otitis media trial with a baseline tympanocentesis, what is the most informative repeat tap? Is it the tap that's done at the on therapy visit? Is it a tap done at the end of therapy? Is the appropriate timing a tap done at the time the patient clinically fails or should it be some combination of the above?

Question three, in an acute otitis media trial targeting PRSP, is a lower clinical cure rate for PRSP acceptable compared to cure rates in an all comers trial?

And in your discussions and in your deliberations, please provide a lower bound of an acceptable clinical cure rate for patients with PRSP, taking into consideration the natural history of the disease about which we know probably not too much.

Next.

Question four, do the data support the safety and efficacy of Augmentin ES for the treatment of acute otitis media due to PRSP?

If yes, what would be the appropriate role for Augmentin ES in the treatment of acute otitis media? Should that role be as empiric therapy or should there be some consideration of the role being that for treatment when PRSP has been documented?

If no, what additional study or studies would you recommend?

Next.

And last but not least, I'd like to just acknowledge the entire review team, and both for their involvement in the review of the application and also for their assistance in preparation of this presentation.

Thank you.

DR. RAMIREZ: Thank you very much, Dr. Makhene.

We will next go to the FDA breakpoint presentation and then have a discussion addressing questions to the presenters at FDA for both of these presentations, and then present the questions to the committee.

Dr. Altaie.

DR. ALTAIE: Thank you, Dr. Reller.

And good afternoon. I'm Sousan Altaie, the clinical microbiology reviewer on this

application, and today I'd like to take you through the data that submitted by the sponsor to support the proposed breakpoints.

Next slide, please.

As an overview of the presentation, I will take you through a brief introduction, and then I will discuss the sets of data that the FDA examines and requires for the sponsors to submit to set the breakpoints. Those are the data that are used to set the provisional breakpoints, and they include the in vitro antimicrobial activity, the pharmacokinetics and pharmacodynamic studies in animals and in human, and then the efficacy studies in animal models.

After one scientifically guesses or deducts what the breakpoint should be, then one would confirm the final breakpoints using the efficacy data coming from clinical trials.

Next slide, please.

In terms of introduction, the proposed susceptibility breakpoint by the sponsor for the Augmentin ES or the 14 to one ratio is less or equal to four micrograms per mL.

Next slide, please.

To start examining the data for provisional breakpoints, I would like to walk you

through the in vitro antimicrobial activity that was submitted.

Next slide, please.

And these data come from four surveillance data that are quite recent, and they represent what's currently happening with the Streptococcus pneumoniae.

Next slide, please.

Actually all of the data in all four studies are very similar, and I will just walk you through the data extracted for the U.S. isolates of Streptococcus pneumoniae -- there's 1,500 of them -- through '97, '98, coming out of the Alexandria project.

If one looks at the other data, the distribution is quite similar.

This is the frequency distribution histogram of Streptococcus pneumoniae against amoxicillin-clav., and one can clearly see the bimodal distribution of these organisms.

Next slide, please.

If one looks at the global isolate -- there is over 6,000 of them coming from the Alexandria project -- against amox.-clav., one can still again see the bimodal distribution of the isolates. So the isolates coming from all geographic areas still follow

the same pattern.

And, in fact, if one looks at the MIC distribution for penicillin against Streptococcus pneumoniae, one would see the exact same kind of distribution. Otherwise, if an organism is penicillin susceptible or penicillin intermediate, it would also be amoxicillin susceptible or intermediate counting the current FDA approved breakpoints for amoxicillin-clav., which is at 0.5 micrograms per mL at this point.

And that is the breakpoint for the four to one formulation, and these consistent of all of the penicillin resistant isolates. As well, they are amoxicillin-clav. resistant with the current breakpoints.

So otherwise if an isolate is amoxicillin susceptible or intermediate is also penicillin susceptible or intermediate, and if it's amoxicillin resistant, it is also penicillin resistant.

Next slide, please.

To just show you a little bit of numerical values to go with those histograms, this comes from the four studies I mentioned. This is the number of the Streptococcus pneumoniae, and these are separated by penicillin susceptibility.

Otherwise, if one looks at the penicillin susceptible Streptococcus pneumoniae and look at their MICs against amox.-clav., one can see that MIC 90s against amox.-clav., consistently low because they are penicillin susceptible, and it really doesn't matter where one sets the breakpoints, at two or at four. All of them are going to be categorized as amoxicillin susceptible; otherwise penicillin susceptible consistency with amoxicillin susceptible.

Next slide, please.

If one now looks at the penicillin intermediate streptococci and look at the MICs, again, from the same four studies, their numbers are there. And one looks at the MIC 90s against amox.-clav., and they all fall at one.

And, again, it doesn't matter where one sits the breakpoint, at two or four, all of them are going to be categorized as amoxicillin susceptible or treatable.

Next slide, please.

The picture is slightly different when one looks at the penicillin resistant Streptococcus pneumoniae. At this point one sees that the MICs jumps to four and eight, and now it makes a difference where one sets the breakpoint, at two or four. One

would be categorizing penicillin resistant isolates as amox.-clav. susceptible, anywhere between 60 percent to 80 percent of the time, depending on the data set, and if one sets it at four, then we are pushing more of the penicillin resistant isolates into interpretation of amoxicillin-clav. susceptible and treatable.

And I think poses a big problem when one looks at the clinical outcome on this particular isolate and what happens to the patient that had these isolates.

Next slide, please.

The second set of data that was used to set the provisional breakpoints are pharmacokinetics and pharmacodynamic studies.

Next slide, please.

There was two. The first, pharmacokinetics studies in animals. There were two studies presented to the FDA, and they both showed the same result. there was a relationship between therapeutic efficacy and time above MIC.

In the neutropenic murine thigh model, the efficacy was observed when time above MIC exceeded 30 percent of the dosing interval. And in the neutropenic murine pneumonia model, the efficacy was

observed when time above MIC exceeded 40 percent of the dosing interval.

Next slide, please.

The next set of data were pharmacokinetic-pharmacodynamic studies in human, and we already hear Dr. He Sun speak elegantly about the concerns that the FDA has with extrapolated data and the variability issue associated with the PK/PD studies.

But be it as it may, when one plugs in the MIC of four micrograms per mL in this pharmacokinetic extrapolated data, one can obtain 41 percent above the MIC during the dosing interval, and if one plus in a MIC of two in this equation, time above MIC would be approximately 51 percent of the dosing interval.

Next slide, please.

And the other study is the 446, and both studies corroborate with each other. Granted that FDA has a problem with the variability and the consistency of the data and that extrapolation did not pan out.

nevertheless, if one plus in the MIC of four in this extrapolated data, time above MIC is approximately 38 percent of the time, and with an MIC of two is at 50 percent of the time.

Next slide, please.

So now at this point one is thinking what

is the efficacy data for animal models. The sponsor had presented us with one animal model, and this is a respiratory tract infection caused by Streptococcus pneumoniae in rats.

There were three groups of animals in this study: the control untreated; the ones that were treated with seven to one; and the ones that were treated with 14 to one.

And the counts were done in the lungs and the viable bacterial counts were calculated.

Next slide, please.

This is the data coming from that study. The sponsor has used four isolates of Streptococcus pneumoniae per group of animals, and the difference between the isolates is their MICs.

The first group were treated with -- were infected with an organism with an MIC of two, four, and eight, and so on, and when Streptococcus pneumoniae has an MIC of two, it doesn't matter if you treat them with Augmentin seven to one or Augmentin 14 to one. You still get nice eradication of the organisms compared to the control.

You've now increased the MICs to four. Then two has difficulty; Augmentin seven to one has difficulty treating these organisms. There is no

difference between this and this, the nontreated versus treated with seven to one, but the 14 to one still manages to eradicate the organisms.

Granted that less than the previous, but yet still significantly decreasing the numbers.

When one looks at the infective isolates with an MIC of eight, neither seven to one nor 14 to one are able to eradicate the organism. Otherwise the eradication of the organisms are directly related to their MICs. The higher the MIC, the more difficult to clear the organism.

So at this point one is thinking that from the in vitro data one can set the breakpoint at one. From the animal efficacy data, one is hovering around the MICs of two or four.

The proof comes into clinical trials, and -- next slide, please -- and we can finalize the breakpoints based on the outcome.

I'd like to state that the methodologies that the FDA uses has always been a test of cure. We always have looked at the setting of the breakpoints, efficacy rate, a test of cure.

And with that in mind -- next slide, please -- I promise not to take you through study 536 again, but I will just tell you -- talk about a little

bit of the results that are related to how we set the breakpoints.

Next slide, please.

This is the ITT bacteriological efficacy in patients that had Streptococcus pneumoniae alone or in mixed cultures. And this is the span of the MICs.

I actually don't like to set percentages next to numbers when the isolates are less than ten. So I left them blank, but one can in mine see that one across the board can get fantastic bacterial clearance of the organism.

Next slide, please.

When one looks at per protocol bacteriological population, the success rate holds, and all across the MICs one sees high eradication rates. The low numbers are still missing, the percentage calculation.

Next slide, please.

The picture changes when one looks at the clinical response for the per protocol population at test of cure. Remember that breakpoint of one? Right here, the bracket down here.

These isolates are penicillin resistant isolates, as well have MICs of amoxicillin higher than the rest, and the efficacy rates, the nice efficacy

rates tends to break right here.

The efficacy rates are high from 0.16 to one, and they drastically drop when the MICs hit two. And they get really bad at eight even though the numbers are small.

next slide, please.

To discuss the amox.-clav. breakpoints, I'd like to make the following important notes. The clinical success rate for isolates with MICs of less than/equal to one microgram is almost 80 percent. The clinical success rate for isolates with MICs of greater than two, looking at the penicillin resistant isolates altogether, is at 53 percent.

And this is the sponsor's evaluation. This is minus those four patients that Dr. Makhene has a problem with. This is the sponsor's evaluation.

Our evaluation is lower when Dr. Makhene puts in those two -- the four patients that are under dispute between the two evaluations.

To set the breakpoints, I went with the optimistic view of the sponsor, and I'm saying if an MIC is greater than two, this is the efficacy rate. If the MIC is greater than four, the efficacy rate drops even further, equal to -- actually this is equal. The four -- the ones with the four MIC are

included in this population. If the MIC is greater or equal to four, the efficacy rates is at 38 percent, and the same here. If the MIC is equal or greater than two, the efficacy rate is at 53 percent.

Next slide, please.

I'd like to remind you of the amox.-clav. MIC frequency distribution histogram of Streptococcus pneumoniae that indicates a bimodal distribution, and the two populations separate at the current FDA susceptible breakpoints for amox.-clav. that is at .05 microgram per mL.

This breakpoint nicely separates the penicillin susceptible isolates from penicillin resistant isolates. Penicillin susceptible intermediate have amoxicillin-clav. MICs of less or equal to one, and the penicillin resistant isolates have amox. MIC of greater or equal to four.

I believe these two populations should be examined separately when one sets the breakpoints.

Next slide, please.

And this is the bimodal distribution. I'd like to discuss it right on the graph and state that if one sets the breakpoint at one or equal to one right here, include some of the amoxicillin intermediate isolates into the amoxicillin

susceptibles, and that also includes penicillin susceptibles and penicillin intermediates, the outcome from an in vitro susceptibility test would be that this test, when you report a susceptible result to a physician, the physician can expect around 80 percent success rate in their patients.

If one sets the breakpoint at two micrograms per mL, equal to two microgram/mL, we stat mixing the two populations. These are penicillin resistant isolates.

And if one mixes the two populations, the overall success rate is at 75 percent, and if you report a susceptible organism that has an MIC of two against amox.-clav., then you have a physician thinking that they have a success rate of 75 percent in the patient population.

But we know that these isolates have only efficacy of 53 percent by themselves. So I think it's overestimation and misinforming the physician if we set the breakpoints at two and say that they are going to respond clinically the same as these guys, and that didn't pan out in the clinical trials.

If one sets the breakpoint at four, the picture even gets worse. Granted that if you look at the isolates with MICs of greater or less or equal to

four, you have a predictability of 75 percent for that in vitro test to gain success, but the numbers here are very low. The bulk of the isolates reside in these two MICs, and the effect that overall this two and four would have on the entire population is very low.

If one looks at the success rate only in these two populations, the success rate is 59 percent for the isolates with an MIC of two and four.

Next slide, please.

So for discussion, considering the bimodal distribution of Streptococcus pneumoniae and the clinical failure rates for patients with isolates having amox.-clav. MICs of greater or equal to two micrograms, what would be the most informative susceptibility breakpoint for a physician for Streptococcus pneumoniae against amox.-clav.? Would it be equal or less than one? Would it be equal or less than two or less or equal to four?

And the floor is open for discussion.

Thank you.

DR. RAMIREZ: Thank you, Dr. Altaie.

We now would like to discuss both of these presentations. We will have discussions related to the questions specifically subsequently, but right now

questions, clarification of the information presented by Drs. Altaie and earlier Makhene and Dr. Sun from the panel members.

Yes, Dr. Murray.

DR. MURRAY: Just two quick questions, Sousan. All of that is based on test of cure at the 21 to 28-day sort of thing, right?

DR. ALTAIE: That's correct.

DR. MURRAY: Okay. The second question was there was some isolates with amoxicillin MICs, as I recall, of eight, but none with a penicillin MIC of eight. Were those done by the same lab in the same hands?

I'm just curious about that. I think I have --

DR. ALTAIE: I only discussed the MIC breakpoints for amox.-clav.

DR. MAKHENE: Right. I'm sorry. That may not have been --

DR. ALTAIE: Because that's the issue under the discussion. What is the breakpoint for amox.-clav.?

DR. MURRAY: Right. That may not have been for you, but perhaps --

DR. ALTAIE: Right.

DR. MAKHENE: As far as the clinical information in the clinical study, what was submitted were just the 41 that qualified for the PRSP ITT population had either an MIC of two or four. No eights.

DR. MURRAY: But in that group must have been the ones that had the MICs of eight of amoxicillin. I was just curious about that.

DR. ALTAIE: That's correct. Actually I showed that slide where you would look at the MICs by pen resistant. Some of those with the MICs of four and eight amoxicillin, they're all penicillin resistant.

DR. MURRAY: All right.

DR. ALTAIE: If that gets to your --

DR. MURRAY: No, I was just interested in the fact that for a couple of isolates the amoxicillin MIC appeared to be higher than the penicillin MIC.

DR. ALTAIE: It is.

DR. MILLER: Can I just to clarify that? That, yes, there were isolates in that group that had penicillin MICs of four, that had amoxicillin MICs of eight, and those would be considered nonsusceptible then at a breakpoint of four for amox.-clav..

CHAIRMAN RELLER: Yes, Dr. Archer.

DR. ARCHER: Not to beat this dead horse yet again, but there were five patients who had tympanocentesis after therapy.

DR. MAKHENE: After the on therapy visit or in which population?

DR. ARCHER: Yes, after the on therapy visit who were in the penicillin resistant Strep. pneumo. group.

DR. MAKHENE: There were three patients who had it beyond the on therapy visit.

DR. ARCHER: Right.

DR. MAKHENE: There were five altogether in the PRSP group that qualified that had PRSP at baseline and had it on a repeat tap either at the on therapy visit or at some later time point when they clinically failed.

DR. ARCHER: Right.

DR. MAKHENE: Of those five, two had a positive tap on therapy, and the other three had it beyond the on therapy visit.

DR. ARCHER: But in every one of those cases, PRSP group?

DR. MAKHENE: Yes.

DR. ARCHER: Okay. So it's 100 percent of those who failed PRSP that we have a tympanocentesis

on, also grew PRSP, although the data is limited?

DR. MAKHENE: Just those five.

DR. ARCHER: It was 100 percent for the data we have.

DR. MAKHENE: Just those five patients.

DR. ARCHER: Okay.

DR. HARRISON: But one was a different strain than the original. That was the data I heard presented. Is that not true that there were three?

DR. ALTAIE: That's true.

CHAIRMAN RELLER: Dr. Wald.

DR. WALD: Could someone discuss the four discrepancies, the four patients who were interpreted differently by the sponsor and by the FDA?

DR. MAKHENE: Sure, I can, and, John, let me. Slide 62. Oh, it might not be 62 anymore. Okay, yeah.

This is just I summarize the history for each of the four patients here in terms of how -- the clinical course basically. The first patient had purulent otorrhea in both ears, had bilateral perforations and was also noted to have a bulging TM with no mobility that was red and opaque, and then was seen day five and had both TMs still opaque, both of them bulging, both of them still red, no mobility and

otalgia, and then went on to at the end of therapy and at the test of cure had a normal exam.

And as I mentioned in the presentation at the on therapy visit this patient had sterile culture.

Okay. Next.

The next patient -- the first two, just to clarify, the on therapy ones and then the second two are the test of cure ones. So the second patient had right purulent otorrhea and, again, had a perforation; was seen at day four. The purulent otorrhea was still noted at that point, and the TM was noted to be erythematous and opaque; went on at the end of therapy and test of cure to have a normal exam, and his culture at the on therapy visit was sterile.

And as I mentioned, these two patients were the ones that I threw into the bacteriologic eradication because of the negative cultures on therapy.

Next.

Third patient had both tympanic membranes bulging red, decreased mobility; was seen at day six. The left had some decreased mobility, but was noted to be otherwise normal. The right was opaque, bulging, no mobility. Seen at the end of therapy visit; essentially had with is a middle ear effusion and then

seen at test of cure, and his right TM was noted to be opaque, bulging, decreased mobility. The left was normal. His on therapy culture was sterile, and again, because the patient was assessed as a success, there was no taps or anything followed up.

Okay. Next.

The last patient, both TMs were bulging, opaque, no mobility; had otalgia day four. They were still red, but generally the otoscopic findings were noted to be improved.

At the end of therapy visit, essentially still opaque, but neutral position, no mobility in the left, and the right was normal. And at the test of cure, the right was normal. The left was noted to be opaque, red, decreased mobility. Neutral position. On therapy culture was sterile, and that's it. That's the four patients.

DR. ARCHER: Why wouldn't they just be called slow cures rather than failures?

DR. MAKHENE: Yeah, and again, as I said, when I assessed them as failures in the FDA analysis looking at the definitions as they had been defined in the protocol, you know, I guess they could be that.

As I mentioned in my presentation, it could be argued that in terms of the assessment it was

too conservative and too strict in including them as failures.

But following, you know, the protocol definition that failures could be assessed as early as the third day and these patients meeting criteria that showed that they still had what could be considered an otitis at that time point for the first two, and then the other two at test of cure.

CHAIRMAN RELLER: Dr. Chesney.

DR. CHESNEY: I guess this question is for whoever knows the answer.

The test of cure results from the intramuscular ceftriaxone study, I know that they didn't have nearly as much bacteriologic data, but the clinical data, are they comparable to what we're seeing here?

DR. SORETH: There were at least four or five different studies that were part of the package for labeling rocephin for single dose treatment for acute otitis, and let me just focus on two of those. There was a Roche clinical study that compared single dose ceftriaxone to ten days of Augmentin, and I believe that was the Augmentin seven to one formulation.

At week two, that would be as I recall

from the point of randomization. At week two, the response rates for ceftriaxone were -- clinical response rates in an ITT analysis -- 70 percent cure, and that 223 patients out of 320, to give you some idea of sample size, versus an Augmentin success rate of 78 percent, 252 out of 325 patients, with a confidence interval lower bound of minus 15 to an upper bound of minus 0.8. So it didn't cross zero.

And at week four from the point of randomization, those rates fell, as you would expect them to, to 52 percent for ceftriaxone, 168 patients out of 322 successfully treated, versus 63 percent success rate for Augmentin, seven to one, 205 patients out of 327, with a confidence interval ranging from a lower bound of minus 18 to minus 2.6 percent.

Dr. Klein's study was also part of that package, and that was a randomized comparative trial, again, as I recall, without underlying microbiology that compared single dose ceftriaxone to a ten-day course of trimethoprim-sulphamethoxazole. The n for that study was about 600 patients, randomized one to one.

And at week two from the point of randomization, success rates for single dose ceftriaxone, 52 percent versus trimethoprim-sulpha.,

59 percent, confidence interval, minus 16 to 1.2.

And at week four those success rates fell for single dose ceftriaxone, 34 percent versus 44 percent for a ten-day course of trimethoprim-sulphamethoxazole; the confidence interval there, minus 18 percent to minus 1.5.

And that was clinical only. One of the pivotal studies in that package was a noncomparative study of single dose ceftriaxone with underlying microbiology, and if you give me a second, I think I'll find those.

Clearly, I'm not as organized in my back-up slides as Dr. Makhene.

(Laughter.)

DR. SORETH: Hang on just a few more seconds.

In the ceftriaxone package, there was a study performed by Dr. Virgil Howie in which he did tympanocentesis comparing the efficacy of single dose of triaxone to ten days of trimethoprim-sulfa, and the cure rate at 100 -- but it was a two to one randomization. Roughly 100 patients received ceftriaxone versus 50, the comparator.

The cure rate at two weeks was -- clinical cure rate at two weeks -- 45 percent versus 74 percent

fore trimethoprim-sulfa and a cure rate at four weeks of 34 percent for ceftriaxone versus 48 percent for trimethoprim-sulfa, but it occurs to me now that it wasn't simply trimethoprim-sulfa. It was trimethoprim-sulfa in combination with a single intramuscular injection of Bicillin CR.

So a pretty interesting set of comparator regimens.

And last but not least, the Roche bac-T study, which was indeed noncomparative, and this is bacteriologic results. Okay. So what I've just given you was all clinical results, but switching for the moment to bac-T results in that noncomparative trial, the success rates for ceftriaxone broken down by pathogen are given either two weeks from the point of randomization or four weeks from the point of randomization, single dose ceftriaxone.

At two weeks, we know we had a total of only eight isolates of PRSP, and the success rate -- eradication rate there, 65 percent with a confidence interval around that point estimate of 25 to 92.

For pen. susceptible, 30 isolates in the study. A success rate or -- I'm sorry -- eradication rate of 90 percent, a confidence interval around that point estimate, 74 to 98, and for H. flu., 15

isolates, beta-lactamase positive, eradication rate of 86 percent with a success rate of -- I'm sorry -- with a confidence interval around the point estimate of 60 to 96 percent.

And finally for M. cat., beta-lactamase positive, 14 isolates, a success rate of about 80 percent, and a confidence interval of 50 to 95 percent, and if you look at the values that I just gave you, which for the three major pathogens range from 80 -- I'm sorry -- from the lowest, 65 percent for the small group of PRSP patients up to the 90s for other susceptible isolates.

You see in the later time frame of four weeks from the point of randomization lower numbers, just what you would expect. The success rate for those three patients with or -- I'm sorry -- the eight patients with PRSP falls, again, to 38 percent, and it falls anywhere from, you know, ten to 20 percent for other isolates as well.

So a long-winded answer to your question, but I hope that gets to the point.

CHAIRMAN RELLER: Dr. Murray.

DR. MURRAY: Just could you remind me why -- what led you to use this the time of cure -- test of cure? Why set that as opposed to the end of the

therapy or the other two? What were the factors, or is this presented because the other data were being presented by the sponsor?

I mean, I realize there were three different time points, but how did you -- what was your process in deciding that one was perhaps more relevant than another?

DR. SORETH: I think the simple answer to your question, Dr. Murray, is that we were following the guidance document which we had discussed, we thought, at length in a couple of committee meetings, and right or wrong, that's what we were going with, and we knew the sponsor was going to be looking at the other endpoints and putting their money, so to speak, on clinical cure at a time point at the end of therapy and key bacteriologic assessment at that on therapy tap.

But I think it really forms so much of the basis why we're here today. We had a guidance document, as I said, discussed at length with the committee in public, commentary invited from industry and academia and so forth, with an imprimatur, as it were, on that draft guidance to look at clinical assessment at test of cure, defined a couple of weeks beyond the last dose, and to assess bacteriologic

outcome, to take a look at it on therapy, but as I pointed out in my slide, our guidance document reviewed several times stated that it would be -- the on therapy tap would be reviewed as basically one of, you know, interest, but one that could still represent suppression of bacteria.

And I think if that's right or wrong is the substance of, you know, much of our discussion and our focus.

DR. MURRAY: And the previous meetings, which I don't think I was involved in any of those at the time -- but, I mean, so the sense was that the late test of cure would be of interest to look at, but it wasn't necessarily the conclusion that this was the proper time point that should be the evaluation?

So you're still asking that question. I realize that, but was the previous sense of the committees that that was a very strong, definite time point or it would be of interest for this to be evaluated in future studies?

DR. SORETH: My understanding of the previous meetings, and I have to admit I was at all of them --

(Laughter.)

DR. SORETH: And so were you, Dr. Reller,

and so was Dr. Chesney.

My understanding is that the test of cure was still thought to be -- the test of cure for clinical outcome, you know, roughly two to three weeks off therapy would be the time point to look at for assessment of what was going on clinically with those children, and that's in an all comer setting. There is no enrichment for PRSP.

DR. RAMIREZ: I think one of the difficulties with this in the earlier discussions is how important and how good a predictor the on therapy bacteriologic results are may depend on what category of antimicrobials one is assessing.

Is that a fair statement, Dr. Giebink?

DR. GIEBINK: Well, that was exactly the question I wanted to ask. The subject of bacterial suppression has come up several times today, and the way I just heard it is that you were alluding to something that sounded a lot like bacterial tolerance.

Now, maybe the three of you or more that were actually part of that discussion could talk about what you were thinking when you used the phrase "bacterial suppression," because I don't see anything wrong with suppression unless you're dealing with a tolerant organism that is going to regrow when the

drug is reduced.

And I absolutely agree with you, Barth, that this is totally dependent on the class of drug that we're talking about.

So could we just hear some more discussion about what happened in this discussion of bacterial suppression? What were you thinking?

DR. SORETH: As I go back through the transcripts, I don't think there was a heck of a lot of discussion about it. Dr. Craig is agreeing with me.

And very simply put, the idea was that there is enough antibiotic on board in that middle ear fluid sample to suppress the growth of bacteria in culture, but let the patient go out some time point after therapy ceases and antibiotic ooze out of the middle ear fluid and go away, and those bacteria which you couldn't demonstrate were in the middle ear fluid on therapy then grow up.

That's my take on that discussion, but it was a very small discussion.

DR. CRAIG: Right. I think the primary thing that had us discussing things again was the letter that the CDC working group submitted to the FDA about their concern about using the previous IDSA/FDA

guidelines had possibly resulted in the approval of some drugs for which they thought from double tap studies that there was little efficacy.

And so that's why the tapping study was brought up, was more to make sure that what was coming across from the clinical trials was also showing a bacteriologic response.

DR. GIEBINK: Let me just stay with this for just a second, Barth.

Since I was a part of the CDC working group on that, I do distinctly recall that discussion, and at no time in that discussion did we talk about bacterial suppression. We did talk about the value of two tap studies, and the fact that certain antimicrobials we felt had been approved without bacteriologic evidence, but not bacterial suppression.

And the other last comment on this is that in all of the animal modeling studies that have been done with antibiotic effect, bacterial eradication, we don't have clinical cure there, but we certainly look at bacterial eradication. I have never seen regrowth of bacteria in a chinchilla or gerbil ear.

CHAIRMAN RELLER: Dr. Wald.

DR. MURRAY: Barth.

CHAIRMAN RELLER: Dr. Murray.

DR. MURRAY: I mean, I assume that suppression must have meant that the numbers were below the level of detection, which would probably be very easy to do, but it doesn't mean that every last organism is eradicated.

Tolerance, actually you should be able to grow it. When we talking about tolerance, it means it's inhibited, but not killed. So then you take away the antibiotic, and I would expect that to regrow.

There's also the phenomenon that's been touted these days about the VBNCs, the viable but non-culturable bacteria. I'm not sure I know exactly what to do with those, in any event.

I read the FDA analysis first. I was imagining the organism in some nidus equivalent to a foreign body, not in the medium and not being accessible perhaps to culture, but I could envision them being killed below the level of detection, but still there being organisms present.

CHAIRMAN RELLER: Dr. Wald.

DR. WALD: I would say the two models of infection in which we conventionally do an assessment while the patient is on antibiotics are the ones that were mentioned earlier: urinary tract infection and meningitis. In both cases, we expect the sample to be

sterile, and we understand that they are sterile in the context of there being a lot of antimicrobial on board. That is the expectation.

That tell us there's sufficient antibiotic on board to prevent the growth of the organism, which is the design of our antimicrobial therapy.

So I think that outcome, sterility on therapy, tells us a very important piece of information.

CHAIRMAN RELLER: Dr. Archer.

DR. ARCHER: Somebody help me with this, but I remember an article that was in JAMA or somewhere talking about biofilm in the middle ear versus planktonic cells, and that the biofilm growth might be a source for relapse or failure of therapy.

Is this -- does anybody know anything about this concept? And is this maybe something that is like tolerance of failure of therapy, or is this now a totally rejected concept?

DR. ALTAIE: I'd like to address that. I believe in the biofilm issue that when you treat organisms, you kill the planktonic organisms, thereby the patient feels better, but then the biofilm you don't touch, and then they grow and planktonics are released again, and those are nicely demonstrated

where you cannot actually culture them because you can't break them apart.

And when you culture them, they grow as clumps, as a colony, and you are underestimating the number of the bacteria.

DR. GIEBINK: There is an active line of research by DR. Garth Ehrlich looking at exactly this issue in animal models of otitis, but I think it's been pretty well summarized what the state of that art is right now.

CHAIRMAN RELLER: Dr. Marchant.

DR. MARCHANT: In the interval between end of therapy and the 28-day, whatever, test of cure, when the same organism appears, which I showed this morning is the minority of the time, there are at least three possibilities.

One is that idea of suppression.

Another one is that it's been eradicated from the ear, but not from the nasopharynx and then again infects the patient.

And number three is the patient is still living with the same brother or sister or playing with the same day care playmate and gets it back from them.

So there are at least three possibilities for what's going on there, but we should always

remember the data, including the data from Dr. Leibowitz and Dagan in the PRSP era that says that still new organisms, new infections outnumber those relapses, whatever the mechanism of those relapses.

CHAIRMAN RELLER: My recollection of those past meetings, and Dr. Giebink has put his finger on it, is the importance of the useful information in this clinical entity of having double tap studies so that one knew, even though it's a smaller number of patients, exactly what's going on, and the failure to eradicate based on culture on the on therapy -- and Dr. McCracken can speak better to this than I -- it's not good to have meningitis and have viable organisms on therapy.

And the data presented here, I think, validates the importance of the emphasis on these double tap studies. When there are no organisms, the patients did well. There may be organisms and they still do well, but early recovery with the same organism in those who you couldn't recover it in that three to six-day window, we didn't see that.

For Dr. Altaie, the questions that we're going to address having to do with interpretation of success, bacteriological, clinical, of necessity also involves the breakpoints. There have been some

changes in NCCLS criteria in recent years in response to the emergence of penicillin resistant pneumococci as an important clinical problem.

The break point that you referred to with the four to one combination of .5 that's in the package insert, that was established before the recognition of the current prevalence of penicillin resistant pneumococci?

DR. ALTAIE: I believe so. That's an old application.

CHAIRMAN RELLER: Right. I think this is one important point to get on the record.

The second is if one were to take, let's say, 100 pneumococci with MICs distributed between -- for penicillin -- .25, .5 up through eight, and did on the same isolates by same standardized methodology MICs to amoxicillin, what would be the shift, if any? Would they be exactly the same? Would they be on balance one dilution difference one way or the other? What would that show?

DR. ALTAIE: Actually one of the slides I showed would show that. If John would bring it up, I will numerically discuss it with you.

John, it's slide number ten.

These are penicillin resistant isolates.

Their MICs are greater than two, equal or greater than two, and the MIC 90 for amoxicillin-clav. is at four and eight.

For some reason when you look at the penicillin resistant isolates, you don't see MICs against amox.-clav. at two. It jumps from one for penicillin intermediates, the slide before this, John.

If you look at penicillin intermediate isolates, their amox.-clav. MICs is at one coming from all four studies consistently, and you don't see MICs of two against amox.-clav. when you look at penicillin resistant isolates.

So if you're looking at penicillin intermediate and penicillin susceptible, the histograms are almost on top of each other. Once you look at the penicillin resistant isolates, you are off with one dilution. Otherwise the amox.-clav. isolates have higher -- the penicillin resistant isolates have one dilution higher amox.-clav. MICs.

So the two is skipped.

CHAIRMAN RELLER: Thank you.

Dr. Jacobs, you wanted to make a comment on this issue.

DR. JACOBS: Yes. Some of those points made in your answer I don't believe are correct. When

you look at MIC distributions, when you look at a histogram between penicillin, amox., and amox.-clav., they look pretty similar.

What you find when you look at it in more detail though, as you've seen, is there are more amox. eights than there are penicillin eights, sometimes even 16, and when you specifically take penicillin resistant strains, which have MICs typically of two and four micrograms per mL, their amoxicillin and amox.-clav. MICs vary between one and eight, and the amox. MICs of eight typically have penicillin MICs of anywhere between one and four.

And the reason for this is probably that the binding to the different PBPs or the affinity of the binding is different between penicillin and amoxicillin.

So I'm not sure that this gets us anywhere, but the explanation is that because of these differences in PBPs, you do see slight differences in MICs, and looking at MIC 90s doesn't really give you that answer. It doesn't give you enough detail.

But it's not unusual to have a strain with a penicillin MIC of one or two and an amoxicillin MIC of eight.

CHAIRMAN RELLER: I wanted to -- yes, Dr.

Chesney.

DR. CHESNEY: Sorry. A comment and a question of Dr. Marchant.

The comment. I was involved also in the double tap discussions, and my memory is as Dr. Craig's, just for Dr. Giebink's interest. I don't remember discussing bacterial suppression.

But my question is: does the relapse rate in this study alarm you, test of cure, Dr. Marchant, compared to some of the other studies that you reviewed for us?

DR. MARCHANT: No. Basically these studies, when you get a lot of high risk patients that have had recurrent otitis media that are young that are in day care, that have had previous antibiotic exposure, you're going to see a lot of recurrences after therapy. The numbers make sense to me in that context.

And one of the problems of the enrichment and the selection of PRSP is you're selecting patients. You're not just selecting organisms. You're selecting patients who are also at high risk for recurrence by doing that.

So you have confounding that's very remarkable. So I don't think any of the rates at the

so-called test of cure are alarming in any way, and of course, I think that we ought to be looking back at the earlier endpoints to find out what's really going on.

DR. LEGGETT: Can I address this? A clarification.

CHAIRMAN RELLER: Go ahead.

DR. CHESNEY: Just one thing. That includes relapse. I mean, as far as we know some of the organisms were the same, but that's not more than you would have expected.

DR. MARCHANT: No.

DR. LEGGETT: A clarification of this point. When I look at Dr. Makhene's data, there's slide number 24, which shows that the demographics for less than 18 months and prior antibiotics, which I assume is also an episode of acute otitis, is higher for the PRSP intent to treat.

Then when I go to slide 30, or on page 15, and I agree it's only pencil and paper math here, but if I look at the MICs less than or equal to one who have those risk factors, there are 78 out of 109, or about 72 percent have the same risk factors for recurrence, in other words, less than 18 in prior acute otitis, as the MICs greater than or equal to

two, which albeit was 88 percent, had those risk factors versus 72.

But with that, the MIC greater than or equal to two only had about a 30 percent response rate. The MIC less than one had a 50 percent response rate. So I'm not sure it's the population that's different based on what has been identified to us here solely on the basis of younger kids with siblings causing more relapses or reinfections.

CHAIRMAN RELLER: Dr. Ramirez wanted to make a comment earlier.

DR. RAMIREZ: I just want to ask regarding the test of cure and clinical outcome, end of therapy. It seems to me we hear a lot of criticism about all the problems, about looking at outcomes at test of cure because of the problem of reinfections. What are the criticisms, if any, to looking at outcome at end of therapy?

DR. MURPHY: I think one of the issues we try to point out is that the earlier discussions really were addressing all comers trials, and that we also need additional information. We have limited double tap studies to make sure that we'd like to have organisms that bacteriologically eradicate, can't grow, whatever terminology we want to use now.

I think what we're presenting you today is that we're not saying that that is unacceptable. We're saying that everyone needs to recognize if that is decided by the committee or they feel that that would be the correct test of cure, that you are in this type of study, this enrichment study we are selecting for a very high risk population; that the way you change your answers is you change your population, and that you are going to have different cure rates if you do that than if you look later.

We felt because the population in all comers shouldn't be relapsing, shouldn't be recurring, you wouldn't expect to have high failure rates at that test of cure. If you're picking a different population, you may be having higher failure rates.

So I guess that's a backwards way of saying we don't think that that's an unacceptable endpoint. We're asking for the discussion about why you would or would not recommend that as an endpoint in particularly these type of trials where you're targeting resistant organisms.

DR. JACOBS: But explain this just for my education. If I understand, the data that was presented this morning was not on enriched studies. It wasn't --

DR. MURPHY: The micro was.

DR. JACOBS: But I say that the data that at the end, at test of cure, there was the new infection. Are these only special populations or these were just --

DR. MURPHY: Yes.

DR. JACOBS: These are special populations.

DR. MAKHENE: I'll let the sponsor probably answer, but essentially the data that was presented is the same. The emphasis was just --

DR. JACOBS: No, I'm not talking about the data with the Augmentin. I'm talking the data from the literature.

DR. MAKHENE: Oh, okay.

DR. JACOBS: I understand that all of the data for the literature in every or most of otitis media studies, if you wait for 30 days, you have a lot of new infections.

Now, it seems to me regardless of the population, will we have the problem of new infection if we wait 30 days. Then I've been educated today over all the problems that we have if we wait 30 days.

Then I know what is the problem, but I would like to see if there's any problem just to get

all comers and look at end of therapy. We can do the retap, but this is different.

I would say just look at clinical outcomes, just at the end of therapy. What would be the problems if I develop a clinical trial for otitis media that I said that, okay, my clinical outcome is going to be for all comers at the end of therapy?

CHAIRMAN RELLER: Dr. Ramirez, we're going to come back to that with question one because this is one of the things that the FDA would like the committee's assessment of and recommendations.

Now, let's continue with questions that would be the database on which the subsequent discussion and votes will take place.

Dr. Craig, did you have something you wanted to say along those lines?

DR. CRAIG: Well, I was just going to comment that I think one of the reasons why the committee before kept the to look at the test of cure was that without a tap, you really don't know what the bacteriologic status is, and so if you're assuming it's presumed the bacterial eradication at the end of cure, we didn't know that for sure.

And so by looking for a longer time to see if there was a relapse was one of the reasons, I

think, why we kept it there.

However, if you've done a tap and you know the organism is gone, now, you know, looking longer, as you say, just gets into all the problems that all the studies have shown of new infections, new colonizations, things like that.

But without the tap, you really don't know what the bacteriologic status is without those double taps.

CHAIRMAN RELLER: Dr. Archer.

DR. ARCHER: Dr. Wald brought up the example of urinary tract infections. When we look at urinary tract infections, we measure test of cure by whether somebody relapses. We could reculture their urine up to two weeks after an upper tract infection to differentiate relapse and reinfection.

Those people who study otitis, is there something different about otitis that we don't expect relapse to occur in this kind of an infection as we would in an upper tract urinary tract infection? I mean, is there any reason why we shouldn't apply the same criteria?

DR. HARRISON: Just real quick, doing it again, as was brought up, if you have a child who's well who's gone through a tap and is coming in for the

visit and you say to Mom, "I just want to tap to see if there's anything still in here. I know he's well, but I want to tap it," it's not a well received procedure.

(Laughter.)

DR. HARRISON: There is a way to do that, and I've suggested this a couple of times, would be to take the children who are otitis prone and scheduled to get their PE tubes, and when they get their next otitis, you randomize them to a drug with the idea they're going to get their tubes put in ten to 12 days later, and pull the specimen out then.

But it's a complicated algorithm.

DR. ARCHER: Well, I understand that, but I mean, if somebody who's been treated for an upper tract UTI comes back in two weeks symptomatic, you expect there's going to be about an even break between relapse and reinfection, depending on the population, and you would culture them and expect that some of those would be relapse, and if they're more resistant, you'd expect more of them to be relapse than reinfection.

Is that not the same criterion you should apply to otitis or is there something different?

DR. HARRISON: Well, that's what actually

the guidelines say, is that failures should be tapped again to see what they are, and that's built into the studies.

But if you've ever done these studies, still you have parents who opt out of the second tap, even though they sign up to do it in the first place. At least that's been my experience.

DR. MARCHANT: Depending on the populations studied, the recurrence rates are often 27, 28 percent in the large Pittsburgh study. In some of the studies where there are younger patients, they go up above 30 percent that are recurring within a 30-day period from the onset of therapy. So they're very common in this disease to have a recurrent episode.

And we've talked about all the risk factors for it, and then when we look at the bacteriology of those, all the data that we have so far says there's more reinfections and relapses.

DR. ARCHER: But that was in the pre-PRSP ear. So --

DR. MARCHANT: No, but the third study that I showed this morning by Dr. Leibowitz and Dagan for Israel is done in recent years during the PSP/PRSP era. So it's still happening.

I agree that you might get a slight

increase, some increase when you have a lot of resistant organisms, that probably relapses would go up a little, but there's still the noise of the reinfections overwhelming those.

DR. HARRISON: Can I just make one more comment about that?

I think one of the things also to keep in mind is that the predictors of the drug resistant pneumococcus, the resistant organisms are exactly the same as in recurrent otitis media, and when the rural Kentucky group looked at their patients who had the high resistant pneumococci, that that was a predictor of being otitis prone for the next six months.

So that I think that apparent dose response thing you see as the MIC goes up may not be due to the MIC of the organism at the time of the acute infection, but due to the underlying problems with the host that predisposed to them getting it in the first place.

CHAIRMAN RELLER: Before we address the questions, additional clarification, I think, may be helpful, and that has to do with what the current published breakpoints are by the NCCLS, and I'll ask Dr. Craig to refresh my memory if I don't get this exactly right.

But in January 2001, the document that licensed laboratories in this country are supposed to use in clinical practice, the MIC for amoxicillin, amoxicillin-clavulanate acid without regard to the ratio in the clinical preparation that is to be given, nor the dosing, I mean, it figures into the breakpoints, but it's not delineated as to the breakpoints.

In other words, there's one breakpoint, and that is susceptible is two micrograms per mL or less; intermediate, a four; and resistant, eight.

In the current documents, there is only a breakpoint based on what is required for therapeutic efficacy in meningitis with penicillin and those breakpoints familiar to everyone here are .06, intermediate that's susceptible, intermediate .12 to one, and resistant two micrograms per mL or more.

In next year's edition, in January 2002, assuming no changes by the NCCLS voting committee, there will be meningitis breakpoints, which are the same as they have been, and breakpoints for non-meningitis indications.

And those non-meningitis breakpoints will be basically a simple way to look at it is shifting down one category. So susceptible is what was

inclusive before of intermediate strains with regard to penicillin. The resistant becomes intermediate, and then resistant at four micrograms per mL or more of penicillin.

Correct, Bill?

DR. CRAIG: No. Penicillin MICs did not change. The only thing we changed were ceftriaxone and the cefataxi (phonetic). Penicillin is still kept there mainly because a lot of other drugs are fed off of it that do not have separate breakpoints.

So we still kept penicillin exactly as it was.

CHAIRMAN RELLER: Right. Thanks.

What I should have said is the document though persists in delineating that the intermediate strains, which are .12 to one, can be treated with appropriate doses of penicillin in non-meningitis locations. So that in effect, one has resistance at two or more.

Now, to me this fits nicely with what we've heard before having to do with when one gets out to the less susceptible based on penicillin binding protein alteration or absence or loss that, in general, there is going to be about a one tube often shift.

So that what would have a MIC to penicillin of two may have an MIC to amoxicillin of four, and the original breakpoints in the package insert for amoxicillin at .25 were, as Dr. Altaie pointed out, before the recognition of widespread or the existence in this country of widespread resistance to pneumococci with penicillin.

Yes, Dr. Harrison.

DR. HARRISON: When we hear these MICs as penicillin is higher than amoxicillin, the immediate assumption is that that means that penicillin would be better than amox. I'm just saying if you just looked at MICs, and everybody knows, to remind everybody, that it has to be taken in the context of the concentrations that can be achieved in vivo, not just in vitro.

So that relative MICs don't translate one to one, penicillin to amoxicillin necessarily, depending on your site of infection.

CHAIRMAN RELLER: No, actually the point, I think, being made is that the efficacy rates of what you see with -- put simply, the efficacy rates with MICs with amoxicillin of two in time above the MIC with the doses given is totally consistent with the concept of treating those strains that previously were

categorized as penicillin resistant, but in non-meningitis could respond with appropriate pharmacodynamics dosage, et cetera.

So that actually I think the new breakpoints are more in keeping with the clinical results in PK/PD data that Dr. Craig and others have discussed.

So we're moving toward, I think, consistency from looking at it from different perspectives.

Yes, Dr. Ebert.

DR. EBERT: A methodologic question. There appears to be some data with certain drug classes, such as the fluoroquinolones that suggest that MICs may be different when tested by broth-based versus ager-based methods. Does anyone here know whether that, in fact, also happens for the beta-lactamase with amoxicillin or cepholosporins?

CHAIRMAN RELLER: I mean, the breakpoints are not different by methods, and I think one of the great efforts of the NCCLS is to try to make whatever quality assurance consistency of testing products, et cetera, so that an MIC by standard methodology, be it broth or ager, with these organisms would give you the same answer.

Dr. Poupard, do you agree with that?

DR. POUPARD: Yes. I was just going to add that the only difference might be one tube with ager dilution versus tube dilution, but the beta-lactams are not in that same category. They tend to be consistent.

CHAIRMAN RELLER: Okay. I think maybe the time now is for a brief break, and we'll come back and deal with the questions directly.

We'll meet back at 3:45 promptly. That's just over 12 minutes.

(Whereupon, the foregoing matter went off the record at 3:34 p.m. and went back on the record at 3:49 p.m.)

CHAIRMAN RELLER: The FDA has prepared questions that they specifically would like to have the Advisory Committee address. They're in two categories, some for discussion and our perspective only, and others for a recorded vote.

In each of the questions, we'll have discussion and then the vote or that will be the end of it for those with discussion only, and Dr. Soreth will formally present the questions one by one to the committee.

Dr. Soreth.

DR. SORETH: Thanks, Dr. Reller.

The first two questions really concern the issues of clinical trial design, outcome assessment, and the timing of those assessments.

Question number one: to assess the clinical response in an acute otitis media trial targeting PRSP, what is the relevant test of cure? Is it the end of therapy, a few days after the last dose, or later follow-up, say, one to three weeks after the last does?

And would your answer be any different in a trial of all comers, not enriched for PRSP?

The second question, on the micro endpoint, to assess microbiologic response in an acute otitis trial, again targeting PRSP -- I left that phrase out -- with a baseline tympanocentesis, what is the most informative repeat tap, an on therapy tap, a tap at the end of therapy, a tap any time that there's a clinical failure, or some combination of the above?

And, again, we would appreciate it as we revisit our guidance document that you would address this not only for a trial targeting PRSP, but an all comers design as well. We want to get this guidance document straight.

Question number three is one for

discussion. In an acute otitis trial targeting PRSP, is a lower clinical cure rate for PRSP acceptable compared to cure rates in an all comers trial?

Please provide a lower bound of an acceptable clinical cure rate for patients with PRSP, taking into consideration what we know about the natural history of the disease.

And I think after the discussion of endpoints and what you would expect a drug to be able to do with regard to patients who have resistant Strep. pneumoniae, then I think we'll naturally come to the fourth question. Do the data support the safety and efficacy of Augmentin ES for the treatment of acute otitis media due to PRSP, with a yes or no component?

And hopefully if there's time, we'll get to our fifth area that we'd like you to discuss, but not necessarily vote on. Are the current breakpoints -- sorry. Different iteration of the question -- discuss the sponsor's proposed breakpoint of four for Augmentin 14 to one.

CHAIRMAN RELLER: Thank you, Dr. Soreth.

The first question. Discussion before voting on A and B, which could easily be looked at it as A and B, targeting and all comers.

Are there any comments, discussion from committee members before voting?

Dr. Leggett.

DR. LEGGETT: The way I sort of picture it, there are different reasons and rationale for having those two endpoints. The end of therapy gives you a better assessment of the pure drug effect, adherence issues, perhaps absorption of amoxicillin which could be a problem, and I think it should be, rather than a secondary, should become a primary endpoint in terms of the pure drug effect.

But I think there's still a case to be made for a later follow-up which might become a secondary endpoint because it would help identify risk factors for recurrent infection, middle ear effusions. It's probably the more important parameter to the consumer, and that is do they have to go back to the doctor and get drugs again within that month, and it also, as was mentioned earlier today, might incorporate a baseline acquisition of cases over time, especially if the initial cultures were negative, which would allow you at the test of cure to build up a database of what's to be expected, especially as we look at new populations at risk and new pathogens, and it is at present the only data point that allows

comparison to past studies.

So I think that from my point of view you're looking at apples and oranges at the end of therapy, and the test of cure, and you may want to be doing both of them, recognizing that the slant to be given to them may not be what has been the slant to date.

And I think in terms of the acute otitis media for all comers versus enrichment, I'm not sure that there's necessarily a difference, given two caveats. Right now we're on the cusp of what I think are achievable drug levels, and pneumococcus is the most likely to persist and cause the most problems, and so I think that those two are special problems, but not necessarily ones that we should make two different sets of criteria for which we judge adequacy.

CHAIRMAN RELLER: Dr. Ramirez.

DR. RAMIREZ: Let me see if I understand. The question about all comers, this is the way to say that this is going to be the group of patients with otitis media that we're not going to do bacteriology.

DR. MAKHENE: No, that's to basically say that will be the group of patients in which we're not going to necessarily use recruitment strategies to try

to get resistant pathogens. It would just be any child who presents with acute otitis who could have had a recurrence, might not have.

DR. RAMIREZ: I know what you mean by all comers, but some of the data presented today in all comers studies was just clinical studies without bacteriology, and my question is to define if I'm going to do something different in my mind. I have to see because in a study of PRSP by definition is going to be tops, is going to be bacteriology. When you say all comers, are we going to have bacteriology also included or this is going to be let me see what happened. I give you that in two groups. I follow everybody because this is --

DR. MAKHENE: The guidance as it's written now is for two, as Dr. Soreth reviewed this morning, is for any acute otitis media study, including an all comers study to have a clinical study and a bacteriologic study. So there would be some bacteriology collected.

DR. HARRISON: I may have misunderstood, too. I thought I understood, but help me. So no longer will the FDA accept any data that is a clinical study without a tap up front. Is that what I just heard?

DR. SORETH: No. The current guidance document states that what is suggested if you are a sponsor wanting to develop your drug for a claim of acute otitis media is two studies. One study is a comparative trial, which we often refer to as clinical only because tympanocentesis is not required, and in that study, we asked for a tight case definition for acute otitis media, and we asked for -- it's a noninferiority design. You don't get in that study microbiologic information.

The second study that we suggest is one with tympanocentesis at baseline, and in that study typically conducted as a noncomparative trial, there have been studies submitted that have taps day three to five or four to six on therapy. Others, most others did not have taps on therapy. Some have taps at the time of clinical failure, but not all that much data.

So the guidance document still stands, and feel free to comment on that part of it as well. One clinical only study, one study with micro.

It's different from the guidance in '77 where both studies were required to tap all patients enrolled in the trial at baseline.

DR. HARRISON: The reason I said that was

because it sounded like what Dr. Ramirez was asking: couldn't that first study, the comparative study, be an all comer study?

DR. SORETH: Yes. Simply what we mean by all comers is aged from three months to 12 years, and so forth.

DR. HARRISON: I think I understood what you were saying, but I don't think -- I just didn't get that Dr. Ramirez got the answer he was asking for, meaning that if we make a difference for all comers, shouldn't there be a distinction between the all comers who have microbiology versus the ones that don't. Is that what you were asking?

DR. JACOBS: Essentially, yes. I was thinking that in my mind even though all the outcomes that were mentioned are important; I was thinking that if I know bacteriology of the patient, if I have to select one over another, I would probably look for end of therapy as long as I have bacteriology.

But if I have a trial when I don't have any bacteriology, then I would go for test of cure. Then all comers. I would like to see if I have bacteriology that's a matter of all comers. I would like to have it at test at end of therapy. If I don't have bacteriology, if I have to select one, I'd

probably go for the end of or test of cure, the 30 days.

That is an option. There is no cure. The reason I was trying to (pause) --

DR. SORETH: Dr. Ramirez, can I ask you what your thinking is behind that?

DR. RAMIREZ: Well, the thinking seems to be that if we have a repeat tap and these bacteria eradication that was already mentioned, this is the gold standard for antibiotic. We're trying to test an antibiotic. If the antibiotic kill the bacteria, then essentially these are the gold standard.

I would like to do my clinical assessment as close as possible to my bacteriological assessment to prevent any new infection or anything that's going to complicate the data. Then as long as I have bacteriology in my mind, I would like to have the clinical outcome very close to the bacteriological outcome.

If I don't have bacteriology, and I was thinking that there was so many different factors that may influence even the 30 percent that didn't have any bacterial, then I would probably go to the 30 days and put everybody in the same back and say, "Okay. Let me compare the 30 days," assuming that I have patients

without bacteria infection, patients with viruses, patients with -- this is what I was (pause) --

DR. SORETH: I guess I'm confused because I don't see how that assessment at test of cure then a month or so out would be less confounded in the setting where you didn't have bacteriology. It would seem to be just as confounded.

What we were trying to get at in going to a paradigm where we had a clinical study without microbiologic underpinning was simply really a response to sponsors telling us that it was getting increasingly difficult to have two adequate and well controlled trials in which every patient was subjected to tympanocentesis.

And so to that end, we thought go with one micro study, a clinical only study that would address a rigid case definition for acute otitis media based on studies that looked at or validated that combination of signs and symptoms that then added up to be rigid case definition with proven, in high percentages, proven bacteriologic etiology.

So in that setting then of a rigid case definition in a clinical only trial, assuming that the vast majority of patients had microbiologic etiology for their infection, though to make the conduct of the

trial easier it was not documented in each specific trial.

So in my mind, I guess, I don't quite see the logic of having a different test of cure if you have a microbiologic underpinning and tap at baseline, tap on therapy versus a clinical only.

CHAIRMAN RELLER: Thank you, Dr. Soreth.

I think we need to focus on the question and the one before us now is put simply: when is the best time to assess when the patient got better?

So this is the timing of assessing of clinical response, whether or not the patient had microbiological studies done with an initial and repeat tap.

Related to the question?

DR. ARCHER: Yes, related to the question. I don't think you can separate clinical at this point from bacteriology. The question is: is there a higher propensity of relapse in PRSP infected patients than the historical data would have us believe for non-PRSP?

If there's no relapse, then the one to three week assessment doesn't make any sense. If it's all reinfection, it's something else.

If, on the other hand, there is relapse,

then you have to assess the patient after stopping therapy, and relapse can only be assessed by bacteriology. So I still think the issue is relapse versus reinfection, and until you have bacteriology to tell you whether PRSP relapses after inadequate therapy or not, you don't know whether the one to three-week follow-up period is relevant or not.

CHAIRMAN RELLER: This will be the opportunity for the committee to say whether they think it should be different or not based on what they feel the data are relative to relapse, reinfection, or don't know.

But in essence, when is the best time to assess the clinical response, just after therapy or at some time much later?

And then thirdly, whether we think there should be any difference in the clinical endpoint interpretation for enriched versus taking unselected patients, all meeting the initial case definition. One of the two controlled studies or the studies being with microbiology and one without, I mean, this being acceptable.

Comments related to the question that the committee is about to vote on?

DR. BESSER: Yeah, I think you have to

look at end of therapy as the appropriate time point for assessing clinical outcome, and if anything, with PRSP and the risk factors that are associated with PRSP, I think there would be more confounding at the three-week visit for that subset of patients.

So I think if your goal is to truly look at the impact of therapy on that case of acute otitis, you need to look post therapy.

If, on the other hand, a sponsor was coming, asking for an indication of prevention of middle ear effusion or something else that occurs later down the road, then an endpoint that was further out would make sense.

But I think that it becomes impossible to compare drugs or interpret drugs if you're not -- the further out that you go.

CHAIRMAN RELLER: Thank you, Dr. Besser.

Now, the persons voting will be the members of the committee, and we have consultants with voting designation this meeting, Dr. Soreth?

DR. SORETH: Yes, we do.

CHAIRMAN RELLER: Do you know who they are?

DR. SORETH: But Tom will have to remind me exactly who they are.

MR. PEREZ: Those individuals that are here as consultants, okay: Dr. Ebert, Dr. Giebink, Dr. Rodvold, and Dr. Danner, as well as all the members of the committee, except Dr. Wald, are voting members of this meeting.

CHAIRMAN RELLER: Dr. Wald, you wanted to state something before the vote?

DR. WALD: What I wanted to state was that if we're asking the question about the bacteriologic effectiveness of the antibiotic, I think it's only fair to ask it at the end of therapy. We can't expect the antibiotic to have an effect two and a half, three and a half, four weeks later, especially on a mucosal surface that we know recolonizes when there are intrinsic factors like eustachian tube disfunction, and again mucosal colonization which are just naturally -- and persistence of fluid -- which are naturally going to lead to reinfection.

CHAIRMAN RELLER: So let's vote as the following. For the primary assessment of clinical efficacy, the vote would be end of therapy or later in the initial round of voting.

Dr. Archer.

DR. ARCHER: As I said, I don't think we know enough about the later follow-up. I don't think

we know enough about relapse versus reinfection. So until we do, I think that the later follow-up is important.

Now, you're phrasing this that we have to go one or the other as the primary endpoint. We can't do primaries and secondaries?

CHAIRMAN RELLER: Well, we could come back to secondary, but I think somehow we have to get off the dime.

DR. ARCHER: Right.

CHAIRMAN RELLER: I mean you either think that one of these is the best way to assess it or the other one is the best way to assess it. So I'm asking for --

DR. ARCHER: Well, I wouldn't want to say end of therapy as the only, and then not do later follow-up. So if I said end of therapy, that leaves out a later follow-up.

I think they're both important, and I don't think later follow-up should be excluded as an endpoint.

CHAIRMAN RELLER: Well, I'd like to suggest that whatever comes out first is the primary. Then we'll ask if the other one should be a secondary, and if nine out of ten say it shouldn't be a

secondary, then maybe they think it's not important at all.

DR. ARCHER: Okay. Well, I would say the primary would be end of therapy. Secondary would be later follow-up.

CHAIRMAN RELLER: Dr. Chesney.

DR. CHESNEY: Primary, end of therapy.

DR. CHRISTIE-SAMUELS: For this infection, end of therapy. For future infections, new infections, reinfections, and relapses, it would have to be later follow-up, but I go with end of therapy.

CHAIRMAN RELLER: Dr. Cross.

DR. CROSS: I would say end of therapy, and especially for the reasons that Dr. Wald, I think, outlined very well.

DR. LEGGETT: Primary is end of therapy, but we wouldn't know about the less than two having different risk stratifications with the ceftriaxone study, nor would we have known about possible differences in the PRSP. So I think we can not throw out test of cure as a secondary endpoint.

CHAIRMAN RELLER: Dr. Leggett is primary, end of therapy.

Dr. Murray.

DR. MURRAY: Yeah, primary, end of

therapy, but I would encourage secondary at the late follow-up with also encouraging tap, a failure at that time point.

CHAIRMAN RELLER: Dr. Ramirez.

DR. RAMIREZ: End of therapy.

CHAIRMAN RELLER: Dr. Soper.

DR. SOPER: End of therapy. It eliminates the confounder of reinfections, which two thirds of the relapses from what I understand are related to this.

It should be timed based on the half-life of the drug, and it also ferrets out the chronic changes that we've been told about that might complicate the diagnosis if you delayed follow-up.

CHAIRMAN RELLER: I believe the end of therapy should be the principal assessment.

Dr. O'Fallon.

DR. O'FALLON: Well, listening to the medical experts, I would say that end of therapy is going to be the one, especially Dr. Wald here. End of therapy sounds like it's the one that probably most carefully measures whatever, the cleaning out of the bugs from the system, if you will.

But I think that in this age of increasing persistence or of penicillin resistant strains and so

on, much more of that coming on, I think we've got to keep on going. So I second the suggestion that the follow-up to the test of cure, the three or four more weeks is important, too, in order to get information about what is happening in this age of changing realities.

CHAIRMAN RELLER: Let's go to the Part B. I'm sorry. I'm sorry.

Yes, Dr. Ebert.

DR. EBERT: Given the Polyanna phenomenon that we talked about, I'm somewhat pessimistic that either one of these is going to show a substantial difference between a study drug and its comparator, and clearly that indicates the need for microbiology studies.

But given these, I would say the primary should be at end of therapy and the secondary outcome is the follow-up.

CHAIRMAN RELLER: Dr. Giebink.

DR. GIEBINK: End of therapy.

CHAIRMAN RELLER: Rodvold.

DR. RODVOLD: End of therapy.

CHAIRMAN RELLER: Danner.

DR. DANNER: End of therapy is primary. As a secondary endpoint later follow-up, but only in

studies that have a comparator. Otherwise I think it's difficult to make sense of that time point.

CHAIRMAN RELLER: Thank you, and I apologize for the neurological ignoring of my left. I think there's a name for that syndrome.

Now, on the second part of the question, later follow-up, could we just reverse around the table and just state by name your name and what you think the role of that should be, important or not important, as a secondary measure.

Dr. Danner.

This is the late follow-up. Is it an important secondary assessment or ancillary assessment or additional assessment?

DR. DANNER: Yeah, I guess I'll repeat what I said, that I think later follow-up is important, but only in studies that have a comparator so that you can make sense of the number because it's conceivable to me that depending on the two drugs you're comparing, that there may be differences at that later time point, and it would be important to know that.

CHAIRMAN RELLER: It may be reasonable and logical to assess whether your primary/secondary evaluations with the caveats that you mentioned would

in your mind differ whether the trial were an enrichment or not. So we could take care of those two concurrently.

DR. DANNER: I think the later follow-up -- you know, I think to me the most important thing is whether it's a comparative trial or not, and if it's a comparative trial, you could look at that later time point whether it was all comers or enriched, but you would need a comparison so you would know what that time point meant. It would balance populations between the two arms.

CHAIRMAN RELLER: Dr. Rodvold.

DR. RODVOLD: I think that the secondary endpoint on the later follow-up is needed, as Dr. Murray and Dr. Leggett said. I think that some of the caveat they brought in are very important.

I think that particular for both types of trials yet, I think it's a moving target of the pathogenesis, what's the impact of resistance yet, and so I think we're still gathering information so we can make comparative other information that we have.

And this is the first time we have enough information to kind of see where we are, particularly in light of penicillin resistance, but I think we still need some non-penicillin resistant and other

pathogens.

So I'd say in both sets of trials, all comers as well as for specifically target trials until we get more data to understand what is the outcomes with these drugs.

CHAIRMAN RELLER: Dr. Giebink.

DR. GIEBINK: I agree that a follow-up about two weeks after completion of therapy is an important secondary endpoint.

I do not agree that it should only be in comparator trials. A facet of that follow-up point that hasn't been mentioned is that it gives you real time data on the demographics and clinical characteristics of the people you just finished studying.

So when you come to generalizing from either that comparator trial or an open trial, you have a basis for generalizing into the population.

So I think that that endpoint is very important for describing more completely your study population.

CHAIRMAN RELLER: Dr. Ebert.

DR. EBERT: This may sound like a recording of Dr. Giebink's statement, but I believe it's also important to characterize the full time

course of the disease to also identify and describe risk factors for recurrence, and also to compare drugs, especially drugs from different classes with regards to their ability to completely eradicate the pathogen.

CHAIRMAN RELLER: Dr. O'Fallon.

DR. O'FALLON: I agree with everything that these guys over here on your left have said. I think that we don't know enough.

I've been sitting here kind of listening to this data, and I'm not sure how much we really know. Everybody was making statements about the recurrence rate, but I'm not sure how well it's all supported and how much it's just we all know.

So let's get some data.

CHAIRMAN RELLER: I agree with what's been said and do not think that whether it's all comers or trying to get difficult patients, especially with the comparative trials. I think you want to have the same criteria, the primary end of therapy and secondary later follow-up.

Dr. Soper.

DR. SOPER: I think it's important to get later follow-up. It seems to me actually it would be more important in those patients that are

bacteriologically studied so you can discriminate between those patients that are reinfected and those patients that relapse, and that if you collect that data without that, you're going to be confused as to exactly what really happens.

But, again, with respect to what's been said about antimicrobial classes, clearly some may be more suppressive than others.

CHAIRMAN RELLER: Dr. Ramirez.

DR. RAMIREZ: Yes. I would agree that to maintain the same primary endpoint, end of therapy, and later follow-up as a secondary endpoint.

DR. MURRAY: Yes, I agree with the later follow-up as a secondary endpoint. I think it's easier for the -- I mean, I think you know what you're talking about better if there is a comparator. I think otherwise the information is made available for the good of mankind, but it may be confusing if it's not in the -- without bac-T or without a comparator.

CHAIRMAN RELLER: That was Dr. Murray.

Dr. Leggett.

DR. LEGGETT: Repeating myself, I think we should have a test of cures, a secondary endpoint for -- and it should be the same between all comers and PRCP, the goal also being to stratify demographic

risks.

CHAIRMAN RELLER: Dr. Cross.

DR. CROSS: I also agree that the later follow-up is worthwhile, both in the enriched and all comers, and that as we heard this morning, this late follow-up was not just for looking at relapse or reinfection, but also the complications, the later complications of the original episodes. I think that's also important.

CHAIRMAN RELLER: Dr. Christie.

DR. CHRISTIE-SAMUELS: Yes. I agree that later follow-up is important for evaluation of clinical and microbiological evaluation of new infections and reinfections with drug resistant Strep. pneumo.

And, no, my answer would not be any different for all comers.

CHAIRMAN RELLER: Dr. Chesney.

DR. CHESNEY: I think the test of cure is good for a secondary endpoint, and I would do it for all comers and for populations enriched for PRSP.

CHAIRMAN RELLER: Dr. Archer.

DR. ARCHER: I agree.

CHAIRMAN RELLER: Now, for question number two, Dr. Archer, and we'll ask each one in succession,

what's the most informative tap or how would you -- how would you --

DR. ARCHER: I think that it --

CHAIRMAN RELLER: What tap data do you want?

DR. ARCHER: It is essential to get a tap at any evidence of clinical failure, no matter what it is. I think that's one of the big confounding problems with the studies we've heard. In those patients who have failed clinically, we don't have any microbiology, and I think that's essential.

End of therapy would be nice, too, but I think that getting bacteriology in any clinical failure, particularly those that are seen at the one to three-week follow-up would be essential.

CHAIRMAN RELLER: Dr. Chesney.

DR. CHESNEY: I think the most valuable tap is the one on therapy and a clinical failure while therapy is being administered. I would have to really think hard about doing it at a three-week follow-up visit when it was considered to be a failure.

CHAIRMAN RELLER: Dr. Christie.

DR. CHRISTIE-SAMUELS: I think on therapy is probably the most important. I'd like to know if the bug has been removed with the appropriate

antibiotic, and again, if the patient has clinical failure, I'd like to know that as well, too, and what organism is indicated and the drug resistance.

CHAIRMAN RELLER: Dr. Cross.

DR. CROSS: I also agree that at the time of clinical failure it is essential to have a follow-up tap, and it's also, I think, important to have a tap while on therapy.

DR. LEGGETT: On therapy and time of failure.

CHAIRMAN RELLER: That was Dr. Leggett.

DR. MURRAY: Murray.

On therapy and at the time of clinical failure, but I have concerns about defining clinical failure at a three to four-week post therapy date as opposed to reinfection. So I'm not sure. The problem is going to be getting those taps as opposed to retreatment.

CHAIRMAN RELLER: Dr. Ramirez.

DR. RAMIREZ: Yes. On therapy and the type of clinical failure.

Now, if I remember right for some of the presentations this morning, on therapy may be from day one until the patient is taking antibiotic. It may be ten day, and there were some presentations that

indicate as you go more than five, six days, you may miss the -- and on therapy is too broad of a definition. Probably maybe we'll need to just specify three to four days or three to five days, not just on therapy.

DR. SORETH: It's usually specified to be study day three to five or four to six.

DR. RAMIREZ: Okay. Then there is a small window.

Yes, on therapy, and time of clinical failure.

CHAIRMAN RELLER: Dr. Soper.

DR. SOPER: Clearly at the time of clinical failure and clearly at the end of therapy because it proves cure, but nobody in their right mind is going to undergo that, and therefore, it's not realistic, and therefore, the next best thing is on therapy.

So I'd have to say clearly at the time of clinical failure, and then the next best thing would be on therapy.

CHAIRMAN RELLER: I think the most important tap is on therapy, but I concur that patients who fail, especially who fail early on, I'd like to know if the organism they had is still there.

Dr. O'Fallon.

DR. O'FALLON: Listening to the -- again, you all are the experts. What I hear is that for sure at failure. That does seem to be no question about that.

The on study it sounds -- well, pardon me.

At failure, as long as they're on treatment, but if it's three or four or ten or 15 days after the end of treatment, then I guess I'm not sure that that that is going to be meaningful.

So essentially we're asking for on treatment and at failure if on treatment. That's what I seem to be hearing from the rest.

No? I'm hearing for both.

CHAIRMAN RELLER: I think what the consensus is, that the on therapy is when the patients are most accessible, and it provides valuable information that is highly associated with success, clinical success, and that patients who fail at the end of therapy or some time later, but especially at the end of therapy, given the further one goes out it is more likely that it may not be related to the drug, but rather reinfection with possibly the same organism from colonized patients or with a different organism or some new strain from the day care center or

whatever, that that becomes increasingly difficult to ascribe to drug failure the further out from treatment one goes.

That I think is the consensus, strong consensus.

DR. O'FALLON: That that sounds what I'm agreeing with.

(Laugher.)

CHAIRMAN RELLER: Dr. Ebert.

DR. EBERT: During therapy and at the time of clinical failure.

CHAIRMAN RELLER: Dr. Giebink.

DR. GIEBINK: The same, on therapy and clinical failure.

CHAIRMAN RELLER: Dr. Rodvold.

DR. ROLDVOLD: The same.

CHAIRMAN RELLER: Dr. Danner.

DR. DANNER: The same.

CHAIRMAN RELLER: Now, question number three is not for a vote, but for discussion. In an acute otitis media trial targeting resistant pneumococci, that is, penicillin resistant pneumococci, is a lower clinical cure rate acceptable compared to cure rates when unselected patients are entered into the trial, other than those meeting, of

course, the case definition?

Provide a lower bound of an acceptable clinical cure rate for patients with penicillin resistant Strep. pneumoniae, taking into consideration the natural history of the disease.

So, Dr. Archer, in your mind, what cure rate do you think approaches natural history with resistant pneumococci? How much would you have to have to think that you had had some effect on --

DR. ARCHER: A multi-part question.

CHAIRMAN RELLER: -- this organism?

DR. ARCHER: I think the first problem is we don't know the natural history of disease with penicillin resistant, and I think that's been made abundantly clear here today.

So I don't think you can take that into consideration.

I think there are different situations. I mean, if there is no other therapy for PRSP, which that may be the case right now, then I think you have a lower threshold for success. VRE would be a good example for that. We had no therapy. Therefore, we accepted, I think, lower success rates in treating VRE than we would with other infections.

If, on the other hand, we have an agent

which has proven to be 80 percent effective against PRSP, then that becomes the gold standard. So I think it's a difficult question to answer.

At the present time, I would say we are close to the point where there is no other therapy, and therefore, there may be lower acceptable limits for PRSP, but we also don't know the natural history.

So I would say I cannot answer this question. So I defer.

CHAIRMAN RELLER: Dr. Chesney.

DR. CHESNEY: My answer is that we don't accept lower clinical cure rates for PRSP in any other PRSP infection. So I don't see why we should accept them for otitis media.

CHAIRMAN RELLER: Dr. Christie.

DR. CHRISTIE-SAMUELS: I'd say based on the information we have today, we probably would have to accept lower clinical rates, but that doesn't necessarily mean that we wouldn't aim for improving this in the future with better drugs.

Regarding the natural history, we know nothing about it, but what we learned today is that the end of therapy treatment with Augmentin as used today, ES, was 77 percent, and the test of cure, 41 percent. So at least, you know, we should probably at

least aim for those numbers or better.

CHAIRMAN RELLER: Dr. Cross.

DR. CROSS: Well, I share Dr. Archer's concern about not knowing enough about the natural history of the disease. However, also, if considerable in vitro and animal studies seem to correlate certain levels with efficacy, I think it's a logical inconsistency to say that if those show efficacy that we would accept a lower cure rate for human trials.

And so I think the bottom line is that there may be at least perhaps in the labeling a way out in terms of perhaps being able to say that something is moderately acceptable, active, or very active.

So I think, in short, I'm having some difficulty in terms of trying to correlate the preclinical data with the clinical data in terms of coming up with an answer to this question.

CHAIRMAN RELLER: Dr. Leggett.

DR. LEGGETT: I think I'd go with what has been said. I think that certainly a lower bound of an acceptable clinical cure rate is above the spontaneous resolution rate of 20 to 30 percent. So that's as far down as we can go.